

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No: 10/810,768
Applicant: William F. Niland et al.
Filed: March 26, 2004
Title: APPARATUS AND METHOD FOR DELIVERING
WATER VAPOR TO A GAS
T.C./A.U.: 3771
Examiner: Danton DeMille
Confirmation No.: 9079
Docket No.: HQS-107US

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF INVENTOR TRaversing CLAIM REJECTIONS
(37 C.F.R. § 1.132)

PURPOSE OF DECLARATION

1. This declaration is to provide support to the statements made in the accompanying Amendment under 37 C.F.R. § 1.116.

DECLARANT'S BACKGROUND

2. The person making this declaration is one of the inventors.

3. I, Owen Bamford have over 25 years of experience as an expert in the field of respiration.

4. I earned a BA in Biological Science from the University of Cambridge in 1968.

5. Subsequently, I was awarded a Ph.D from Bristol University in 1972 for my work in the field of brainstem respiratory neurons.

6. From 1982-1986, I performed research on the development of cardiorespiratory control at the Nuffield Institute for Medical Research at Oxford University.

7. From 1986-1990, I performed research in neonatology, focusing on prenatal and postnatal development of breathing control, and coordination of suckle feeding with breathing in infants at the University of Maryland. During this time I taught developmental physiology of respiration.

8. From 1990-1998, I performed research in development of sensory physiology of respiratory control at Johns Hopkins University. During this time, I managed a pediatric sleep-disorder breathing laboratory and taught pulmonary dynamics at the fellowship level.

9. I have published the following articles in professional periodicals:

(see attached list of publications in Appendix A)

10. From 1998 until the present, I have worked for Vapotherm, Inc. In this role, I have coordinated, analyzed and presented clinical trials of original Vapotherm devices. In addition, I have worked with design team to evaluate and verify individual components, original devices, and subsequent products. I have trained biomedical techs in service on respiratory devices. In addition, I currently work in the research and development section to develop and test product improvements and act as an information resource to clinical product specialists on technical and clinical aspects of Vapotherm respiratory therapy products.

11. By virtue of my education and experience, I believe that I am qualified to make the statements provided herein.

BREATHING GAS DELIVERY TO NEONATES

12. Many neonates, especially premature infants, need some degree of respiratory support to help with lung expansion. Their airways and lungs are delicate and easily injured by excessive pressure or by insufficient humidity. In order to minimize damage to the lungs and airways, respiratory gases must be both warmed and humidified. The ideal condition is 37° C with 90-95% relative humidity, or at least about 40 milligrams of water vapor per liter of air.

13. One respiratory support option for an infant requires complete respiratory support in which breathing movements are created by a mechanical ventilator connected to the lungs through an intratracheal tube.

14. Another respiratory support option for an infant requires less aggressive support by using continuous positive airway pressure (CPAP), where the airway is kept under positive pressure throughout the breathing cycle but the infant breathes spontaneously.

15. Both of these options have disadvantages. Inserting an intratracheal tube is traumatic. Mechanical ventilation, particularly in very premature infants, almost invariably causes some lung damage and scarring, and extubation may fail, requiring re-intubation and further trauma. CPAP requires a gas source with controlled pressure, and a patient interface that makes a gas-tight fit with the airway. The interface is either a mask, which makes access to the patient difficult, or a large tightly fitting nasal cannula, which can cause erosion of the soft tissues of the nose, in some cases needing surgical repair. Adequate warming and humidification of CPAP is difficult without excessive condensation, but essential to avoid airway damage.

16. It has been shown that a high flow of breathing gas given by nasal cannula can in many cases be substituted for CPAP or even mechanical ventilation. In addition, it may be used as a lower-level respiratory support following ventilation or CPAP. However, the high nasal flows necessary could not be administered without adequate heating and humidification, which was not available prior to the presently claimed invention.

17. The Office Action states that "[t]he exact flow rates and humidity levels used during operation of the device is well within the realm of the practitioner of ordinary skill in order to compensate for practical considerations of intended use dependent on the requirements for each individual patient." I disagree. While flows of up to 8 liters per minute could in principle provide respiratory assistance and replace CPAP in many cases, such flows could not previously be administered to infants because of the pulmonary airway damage caused by high flows of breathing gas at less than about 40 milligrams of water vapor per liter. To my knowledge, prior to the presently claimed invention there were no systems available that could humidify flows of up to 8 liters per minute at up to at least about 40 milligrams of water vapor per liter and deliver it through a nasal cannula. Further, in my opinion, modification of available systems prior to the presently claimed invention to warm and humidify high flows of gas (up to 8 liters/minute) to a vapor content of at least about 40 mgs/liter for delivery through an infant nasal cannula would not have been within the realm of the practitioner of ordinary skill.

CLAIMED METHOD

18. Claims 30, 31, and 33 of the present application are directed to a method for delivering heated and humidified gas to, or assisting the respiration of, a neonatal patient. Each of these claims includes the step of "delivering the heated and humidified breathing gas [to a neonatal patient] through the delivery tube assembly and into the nasal cannula at a flow rate of about 1 liter per minute to about 8 liters per minute and at a water vapor content of at least about 40 milligrams per liter."

19. The Vapotherm 2000I device, provided by Vapotherm, Inc., performs the function described in the above step of claims 30, 31, and 33. To my knowledge, prior to the Vapotherm device, no system warmed and humidified high flows of gas (up to 8 liters/minute) to a high water vapor content (at least about 40 milligrams/liter) for delivery to an infant.

20. In one test of the Vapotherm device, the Vapotherm device use was compared with a standard nasal cannula in treating infants following extubation. It was found that "Among NICU patients Immediately following extubation, Vapotherm performed better than a standard high-flow nasal cannula in maintaining a normal appearing nasal mucosa, a lower respiratory effort score, and averting reintubation." See Woodhead DD et al, 2006: Comparing two methods of delivering high flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomized, masked, crossover trial. *J. Perinatology* 26, (8) 481-485.

21. In another test, high flow nasal cannula therapy with the Vapotherm device was compared with conventional nasal CPAP in treating apnea of prematurity. It was reported that "HFNC [Vapotherm device] is as effective as NCPAP in the management of AOP". See Sreenan C et al (2001): High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. *Pediatrics* 107(5):1081-3.

22. In yet another test of the Vapotherm device, a recent study found "High-flow nasal cannula [Vapotherm] use appears safe and well-tolerated. Infants extubated to HFNC spent fewer days on the ventilator. Additional benefits may include a decreased rate of

ventilator associated with pneumonia and improved growth." See Holleman-Duray D et al (2007): Heated humidified high-flow nasal cannula: use and a neonatal early extubation protocol. *J Perinatol.* 27(12):776-81.

23. Vapotherm has been successful in replacing the CPAP and ventilation therapies discussed above with therapy provided using the Vapotherm device.

24. Prior devices for neonatal respiratory support experienced condensation, or rainout, of water in the gas when attempting to achieve high neonatal nasal cannula flows of heated and humidified air. Because high neonatal nasal cannula flows could not be warmed and humidified prior to the Vapotherm device, only low flows could be delivered without severe cooling and drying of the patient airway. The Vapotherm device can warm and humidify a high gas flow (up to 8 liters/minute) to a high water vapor content (about 40 mg/liter) and deliver it through a conventional neonatal nasal cannula. The therapy is delivered without the need for a gas-tight fit to the patient airway. When compared with prior therapies, this innovation represented a new and inexpensive, non-invasive, and non-traumatic option for neonatal respiratory therapy.

25. The Vapotherm device has achieved the following commercial success:

(see attached evidence of commercial success in Appendix B)

TIME AND PRESENTATION OF THE DECLARATION

26. This declaration is submitted after a non-final rejection.

DECLARATION

27. As a person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

28. **Inventor**

Full name of **sole or first** Inventor: Owen Bamford

Inventor's signature: Owen Bamford

Date: 9/22/2009 Country of Citizenship: Great Britain

Residence: 9 Coronet Drive, Linthicum, MD 21090

APPENDIX A

Owen Bamford, Ph.D: selected publications

- 1: Frank SM, Hesel TW, El-Rahmany HK, Tran KM, Bamford OS. Warmed humidified inspired oxygen accelerates postoperative rewarming. *J Clin Anesth.* 2000 Jun;12(4):283-7. PubMed PMID: 10960199.
- 2: Marcus CL, Moreira GA, Bamford O, Lutz J. Response to inspiratory resistive loading during sleep in normal children and children with obstructive apnea. *J Appl Physiol.* 1999 Oct;87(4):1448-54. PubMed PMID: 10517777.
- 3: Sterni LM, Bamford OS, Wasicko MJ, Carroll JL. Chronic hypoxia abolished the postnatal increase in carotid body type I cell sensitivity to hypoxia. *Am J Physiol.* 1999 Sep;277(3 Pt 1):L645-52. PubMed PMID: 10484473.
- 4: Bamford OS, Carroll JL. Dynamic ventilatory responses in rats: normal development and effects of prenatal nicotine exposure. *Respir Physiol.* 1999 Sep 1;117(1):29-40. PubMed PMID: 10505477.
- 5: Bamford OS, Sterni LM, Wasicko MJ, Montrose MH, Carroll JL. Postnatal maturation of carotid body and type I cell chemoreception in the rat. *Am J Physiol.* 1999 May;276(5 Pt 1):L875-84. PubMed PMID: 10330044.
- 6: Wasicko MJ, Sterni LM, Bamford OS, Montrose MH, Carroll JL. Resetting and postnatal maturation of oxygen chemosensitivity in rat carotid chemoreceptor cells. *J Physiol.* 1999 Jan 15;514 (Pt 2):493-503. PubMed PMID: 9852330; PubMed Central PMCID: PMC2269068.
- 7: Gaudia EB, Bamford OS, Northington FJ. Lack of induction of substance P gene expression by hypoxia and absence of neurokinin 1-receptor mRNAs in the rat carotid body. *J Auton Nerv Syst.* 1998 Dec 11;74(2-3):100-8. PubMed PMID: 9915624.
- 8: Marcus CL, Lutz J, Carroll JL, Bamford O. Arousal and ventilatory responses during sleep in children with obstructive sleep apnea. *J Appl Physiol.* 1998 Jun;84(6):1926-36. PubMed PMID: 9609786.

9: Schuen JN, Bamford OS, Carroll JL. The cardiorespiratory response to anoxia: normal development and the effect of nicotine. *Respir Physiol*. 1997 Sep;109(3):231-9. PubMed PMID: 9342800.

10: Gauda EB, Bamford O, Gerfen CR. Developmental expression of tyrosine hydroxylase, D2-dopamine receptor and substance P genes in the carotid body of the rat. *Neuroscience*. 1996 Dec;75(3):969-77. PubMed PMID: 8951888.

11: Bamford OS, Schuen JN, Carroll JL. Effect of nicotine exposure on postnatal ventilatory responses to hypoxia and hypercapnia. *Respir Physiol*. 1996 Oct;106(1):1-11. PubMed PMID: 8946572.

12: Carroll JL, Sterni LM, Bamford OS, Montrose MH. Mechanisms of carotid chemoreceptor resetting after birth. In vitro studies. *Adv Exp Med Biol*. 1996;410:73-7. Review. PubMed PMID: 9030279.

13: Marcus CL, Carroll JL, Bamford O, Pyzik P, Loughlin GM. Supplemental oxygen during sleep in children with sleep-disordered breathing. *Am J Respir Crit Care Med*. 1995 Oct;152(4 Pt 1):1297-301. PubMed PMID: 7551385.

14: Sterni LM, Bamford OS, Tomares SM, Montrose MH, Carroll JL. Developmental changes in intracellular Ca²⁺ response of carotid chemoreceptor cells to hypoxia. *Am J Physiol*. 1995 May;268(5 Pt 1):L801-8. PubMed PMID: 7762681.

15: Vice FL, Bamford O, Heinz JM, Bosma JF. Correlation of cervical auscultation with physiological recording during suckle-feeding in newborn infants. *Dev Med Child Neurol*. 1995 Feb;37(2):167-79. PubMed PMID: 7851673.

16: Tomares SM, Bamford OS, Sterni LM, Fitzgerald RS, Carroll JL. Effects of domperidone on neonatal and adult carotid chemoreceptors in the cat. *J Appl Physiol*. 1994 Sep;77(3):1274-80. PubMed PMID: 7836131.

17: Tomares SM, Bamford OS, Sterni LM, Fitzgerald RS, Carroll JL. The role of endogenous dopamine as an inhibitory neuromodulator in neonatal and adult carotid bodies. *Adv Exp Med Biol*. 1994;360:321-3. PubMed PMID: 7872110.

18: Carroll JL, Bamford OS, Fitzgerald RS. Postnatal maturation of carotid chemoreceptor responses to O₂ and CO₂ in the cat. *J Appl Physiol.* 1993 Dec;75(6):2383-91. PubMed PMID: 8125854.

19: Bamford OS, Rivera A, Tadalan T, Ellis W. Effects of in utero phrenic nerve section on the development of collagen and elastin in lamb lungs. *Am Rev Respir Dis.* 1992 Nov;146(5 Pt 1):1202-5. PubMed PMID: 1443871.

20: Bamford O, Taciak V, Gewolb IH. The relationship between rhythmic swallowing and breathing during suckle feeding in term neonates. *Pediatr Res.* 1992 Jun;31(6):619-24. PubMed PMID: 1635825.

21: Bamford OS, Hawkins RL, Blanco CE. Effects of clonidine on breathing movements and electrocortical activity in the fetal lamb. *Am J Obstet Gynecol.* 1990 Aug;163(2):661-8. PubMed PMID: 2386160.

22: Bamford O, Hawkins RL. Central effects of an alpha 2-adrenergic antagonist on fetal lambs: a possible mechanism for hypoxic apnea. *J Dev Physiol.* 1990 Jun;13(6):353-8. PubMed PMID: 1982117.

23: Bamford OS, Dawes GS. Hypoxia and electrocortical activity in the fetal lamb: effects of brainstem transection and chemoreceptor denervation. *J Dev Physiol.* 1990 May;13(5):271-6. PubMed PMID: 2126795.

24: Hasan SU, Bamford OS, Hawkins RL, Gibson DA, Nowaczyk BJ, Cates DB, Rigatto H. The effects of brain-stem section on the breathing and behavioural response to morphine in the fetal sheep. *J Dev Physiol.* 1990 Mar;13(3):147-55. PubMed PMID: 2277180.

25: Bamford OS, Dawes GS, Denny R, Ward RA. Effects of the alpha 2-adrenergic agonist clonidine and its antagonist idazoxan on the fetal lamb. *J Physiol.* 1986 Dec;381:29-37. PubMed PMID: 2887648; PubMed Central PMCID: PMC1182962.

26: Bamford OS, Dawes GS, Hanson MA, Ward RA. The effects of doxapram on breathing, heart rate and blood pressure in fetal lambs. *Respir Physiol.* 1986 Dec;66(3):387-96. PubMed PMID: 3797850.

27: Bamford OS, Dawes GS, Ward RA. Effects of apomorphine and haloperidol in fetal lambs. *J Physiol.* 1986 Aug;377:37-47. PubMed PMID: 3795094; PubMed Central PMCID: PMC1182821.

28: Jensen A, Bamford OS, Dawes GS, Hofmeyr G, Parkes MJ. Changes in organ blood flow between high and low voltage electrocortical activity in fetal sheep. *J Dev Physiol.* 1986 Jun;8(3):187-94. PubMed PMID: 3745833.

29: Hofmeyr GJ, Bamford OS, Gianopoulos JG, Parkes MJ, Dawes GS. The partial association of uterine contractions with changes in electrocortical activity, breathing, and PaO₂ in the fetal lamb: effects of brain stem section. *Am J Obstet Gynecol.* 1985 Aug 1;152(7 Pt 1):905-10. PubMed PMID: 3927732.

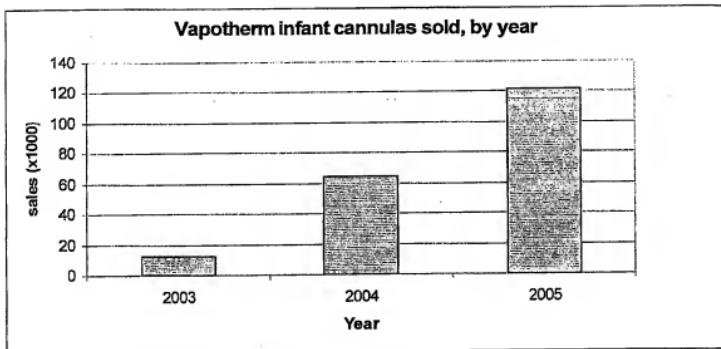
30: Bamford OS, Eccles R. The role of sympathetic efferent activity in the regulation of brain temperature. *Pflugers Arch.* 1983 Feb;396(2):138-43. PubMed PMID: 6835817.

31: Langman VA, Bamford OS, Maloiy GM. Respiration and metabolism in the giraffe. *Respir Physiol.* 1982 Nov;50(2):141-52. PubMed PMID: 7156526.

32: Bamford OS, Eccles R. The central reciprocal control of nasal vasomotor oscillations. *Pflugers Arch.* 1982 Aug;394(2):139-43. PubMed PMID: 7122219.

33: Bamford OS, Maloiy GM. Energy metabolism and heart rate during treadmill exercise in the Marabou stork. *J Appl Physiol.* 1980 Sep;49(3):491-6. PubMed PMID: 7204173.

34: West NH, Bamford OS, Jones DR. A scanning electron microscope study of the microvasculature of the avian lung. *Cell Tissue Res.* 1977 Jan 24;176(4):553-64. PubMed PMID: 832311.

APPENDIX B**Evidence of Commercial Success**

Data for the first three years of sales are shown.

Each cannula sold corresponds approximately to one neonate, premature or infant patient treated with the Vapotherm device. These cannulas are not used with any other device. Thus, approximately 120,000 infant patients were treated in 2005 using the Vapotherm device. Estimated market penetration based on user accounts and total number of hospitals in the USA was about 18% by 2005, only three years after its introduction for infant patients. The customer base for infant care devices is very conservative and there is intense competition from established devices. Thus, this represents significant market penetration in a short period of time given this is new capital equipment with new, previously unknown technology, providing a whole new mode of therapy.